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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,169	HERMSMEYER, R. KENT	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *17-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/4/2008 has been entered.

Claims 1-3, 9, 11, 13 and 15 have been amended. Claims 1-23 are pending, claims 17-23 are withdrawn. Claims 1-16 are examined on the merits herein.

Response to Remarks

The rejection of claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn due to the amendment of claims. Applicants' arguments regarding the rejection of claims 1-16 under 35 U.S.C. 112, first paragraph, scope of enablement has been fully considered and found not to be persuasive. Applicants' amendments necessitated the modified rejections presented in this office action. Applicants' arguments to the scope of enablement rejection have been addressed below. The action is made non-final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for estriol (examples 3 and 4) in a method of treating vasospasm and effect of estriol on diameter of coronary arteries does not reasonably provide enablement of reducing the vascular hyperreactivity in vascular muscle cells comprising exposing the vascular muscle cells with all other estrogen receptor agonist (ER) that has a higher relative selectivity than does genistein for ER-beta compared to ER-alpha and further administering the same to a patient in concert with a hormone replacement therapy. The specification does not teach administration of any other ER-beta ligand other than estriol in reducing vascular hyperreactivity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the Invention:

The rejected claims (1-16) are drawn to a method of reducing vascular hyperreactivity in vascular muscle cells comprising administering to the patient an effective amount of a selective estrogen beta receptor agonist that has a higher relative selectivity than that of genistein for estrogen receptor beta compared to estrogen receptor alpha and administration of the same in concert with a hormone replacement therapy (claims 11-12).

(2) Breadth of the claims:

The clams are broad with respect to the number of estrogen beta receptor agonist compounds as they are drawn to a method of reducing the vascular hyperreactivity in vascular smooth muscle cells. As indicated in the specification vascular hyperreactivity is manifested by different conditions that include coronary arterial vasospasm, hyperactivity of peripheral arteries etc. (claims 2-3). Claims 11 and 12 are directed to reducing the vascular hyperreactivity administering the ER-beta agonist in concert with hormone replacement therapy. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims.

(3) Guidance of the Specification and (4) Working Examples:

The guidance given by the specification to a method of reducing vascular hyperreactivity in vascular smooth muscle cells is 1) comparison of effects of estriol with 3βAdiol and epiestriol in vitro on Ca2+ responses in rhesus coronary VMC (example 9) 2) estriol in a method of treating vasospasm and effect of estriol on diameter of coronary arteries (examples 3 and 4) and comparison of different estrogen beta receptor agonists (genistein, DPN) 3) in measurement of estrogen receptor beta activity.

The specification provides example for comparison of effects of estriol with 3βAdiol and epiestriol in vitro on Ca2+ responses in rhesus coronary VMC, to a method of treating vasospasm by administration of the drug epiestriol and its effect on diameter of coronary arteries.

(8) State of the art:

The prior art teaches genistein and estradiol in a method of treating vasospasm and reducing the incidence or severity of vascular hyperreactivity in a patient. The prior art Meyers, J. Med. Chem, 44,:4230-4251 (2001) teaches the relative affinity of few agonists for ER-alpha and ER-beta. Bhagawat (WO 01/49673) teaches ER modulators, Ohman et al. (U.S 2003/0032779) teaches ER ligands, Barlaam et al. teaches ER-beta ligands (U.S. 6,518,301) and WAY-202196 is a known estrogen beta receptor agonist (see Abstract, Cristofaro et al, Critical Care Medicine, 2006, vol. 34). Lahm et al. (Am J Physiol Regal Integr Comp. Physiol. 295, 1486-93) teaches that selective estrogen receptor alpha and estrogen receptor beta agonists rapidly decrease pulmonary artery vasoconstriction by a nitric oxide mechanism (See Abstract). Harris et al. (Endocrinology, 144, 10, 4241-49) teach an ER-beta selective ligand, ERB-041. The authors state that they expected the compound would be useful in hormone therapy as ER-beta is an attractive drug target for hormone therapy. However, the authors found that the ER-beta selective ligand, ERB-041 is inactive in a large panel of estrogen responsive models and does not prevent bone loss or weight gain after overiectomy (p 4246, col. 2, last para). Also side effects of estriol that has been reported to FDA include contraindication to medical treatment, burning sensation, fungal infections etc

(http://www.patientsville.com/medication/estriol_side_effects.htm, Estriol Side Effects Report #5318690-8).

5) The relative skill of those in the art:

The relative skill of those in the medical treatment art is high, requiring advanced education and training.

(6) The predictability of art:

Despite the advanced training of the ordinary practitioners in the pharmaceutical development and medical treatment arts, the arts are highly unpredictable. The state of the art is such that it is not possible to predict the activity of a compound, whether in vitro or in vivo, based on the structure or function alone. Typically, for the development of a method of treating a disease, a certain pharmacological property of a compound, such as receptor binding or activation, or cytotoxicity, must be tested or verified in an in vitro model. The in vitro activity of a series of compounds must typically be verified individually. In order to predict the in vivo activity of a compound based on the in vitro assay, the assay itself must be definitively well correlated to the pathophysiology of a target disease and verified as being predictive of the in vivo activity of a compound. For example, if a receptor is known to be overactivated in the pathophysiology of a disease, the ordinary practitioner would predict that a compound that inhibits the activation of the receptor may be useful for the treatment of said disease. However, even for in vitro models that involve receptors known to be involved in the pathophysiology of a disease, translating the in vitro efficacy of a compound to in vivo efficacy for the treatment of a disease is notoriously unpredictable unless the correlation has been conclusively

verified. Further, the in vivo efficacy of a compound is not only determined by the affinity or activity of the compound on its target receptor in a validated in vitro assay, but by a range of other factors including the bioavailability of the compound, its pharmacokinetic profile, and the specificity of the compound for the desired target versus other potential targets. It must also be accepted that in vitro testing has its limitations, at least in part because isolated tissues can never fully represent the complex integrated biological systems operating in vivo. The claims of the instant invention are broad with respect to estrogen receptor beta agonists that have a higher selectivity than does genistein for ER-beta compared to ER-alpha. According to Harris et al's studies (Endocrinology, 144, 10, 4241-49) not all selective ER-beta agonists have the same properties. In fact the compound, ERB-041 is inactive in a large panel of estrogen responsive models and does not prevent bone loss or weight gain after overiectomy (p 4246, col. 2, last para) and may not be useful in hormone therapy. Accordingly, it is unpredictable that all ER-beta selective agonists would reduce vascular hyperreactivity in vascular smooth muscle cells and be in concert with the hormone replacement therapy. Also it is known in the art that (Lahm et al. Am J Physiol Regal Integr Comp. Physiol. 295, 1486-93), selective estrogen receptor alpha rapidly decrease pulmonary artery vasoconstriction by a nitric oxide mechanism. Estriol has been found to have side effects in humans (see state of the art, above).The claims are broad with respect to ER-beta agonists and there is a high degree of unpredictability involved. Despite the advanced training in the medical treatment arts, the arts are highly unpredictable.

(7) The Quantity of Experimentation Necessary:

In order to practice the above claimed invention, one of ordinary skill in the art would have to first envision formulation, dosage, duration, route and, in the case of human treatment, an appropriate animal model system to test all the compounds for their selectivity towards estrogen receptors and then whether they have higher selectivity than does genistein for estrogen receptor beta compared to estrogen receptor alpha. Then the compounds need to be tested for their usefulness in a method of reducing the vascular hyperreactivity in smooth muscle cells and in a patient (claims 9-16) comprising administering to the patient an effective amount of the drug. If unsuccessful, one of ordinary skill in the art would have to envision a modification in the formulation, dosage, duration, route of administration etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. Furthermore, one of ordinary skill in the art would have to test the above said compounds in concert with hormone replacement therapy. The specification enables the treatment of vasospasm with estriol and shows comparison of estrogen receptor activities of estriol, 3βAdiol, DPN, genistein and epiestriol. Claim 1 compass a huge number of selective estrogen receptor beta agonists other than the compounds listed in the specification and therefore, it would require undue, unpredictable experimentation to practice the claimed invention of comprising administering every single selective estrogen beta receptor agonist that has higher selectivity than does genistein for estrogen receptor beta compared to estrogen receptor alpha. Genetech, 108 F.3d at 1366 states that “a patent is not a hunting license. It is not a reward for search, but

compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 7, 9, 10, 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hermsmeyer (WO 98/37897) in view of Beaumont et al. (Clin Exp Immunol, 1976, 24, 455-463).

Hermsmeyer teaches a method of treating coronary artery vasospasm, using progesterone and preventing cardiovascular disorder including stroke, peripheral artery vascular disease etc (see p 7, Detailed Description, lines 1-4). The reference teaches treatment of coronary vasospasm comprising administering progesterone topically (see

abstract, claims 1-8). The reference teaches that progesterone can be administered in various routes including oral, topical (cream), nasal, vaginal, parenteral etc (p 11, lines 21-27). The reference teaches administration of 0.1 ng to less than 4 ng/ml of progesterone in treating coronary reactivity conditions (see abstract, claims 3-5).

The reference does not teach an ER-beta agonist compound in a method of reducing vascular reactivity.

Beaumont et al. teaches estriol and progesterone as steroids (Table 3). Epiestriol is known in the art as the epimer of estriol (http://medical-dictionary.thefree dictionary.com/epiestriol).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used estriol an ER-beta agonist in a method of reducing vascular reactivity from the teachings of Hermsmeyer and Beaumont. Hermsmeyer teaches progesterone, a steroid in coronary reactivity treatment and Beaumont et al. teaches the equivalence of estriol and progesterone as steroids. One having ordinary skill in the art would have been motivated in expectation of achieving similar or better therapeutic benefits in vascular reactivity conditions in administering one steroid such as estriol for another steroid such as progesterone. It would have been obvious to one of ordinary skill in the art to administer epiestriol in reducing vascular reactivity in vascular smooth cells because epiestriol is known in the art to be an epimer of estriol.

Claims 1-3, 5-7, 9, 10, 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hermsmeyer (WO 98/37897) in view of Burghardt et al. (Biology of

Reproduction, 36, 741-51, 1987) and Barkheim et al. (Molecular Pharmacology, 54, 105-112, 1998).

Hermsmeyer teaches a method of treating coronary artery vasospasm, using progesterone and preventing cardiovascular disorder including stroke, peripheral artery vascular disease etc (see p 7, Detailed Description, lines 1-4). The reference teaches treatment of coronary vasospasm comprising administering progesterone topically (see abstract, claims 1-8). The reference teaches that progesterone can be administered in various routes including oral, topical (cream), nasal, vaginal, parenteral etc (p 11, lines 21-27). The reference teaches administration of 0.1 ng to less than 4 ng/ml of progesterone in treating coronary reactivity conditions (see Abstract, claims 3-5).

The reference does not teach an ER-beta agonist compound in a method of reducing vascular reactivity.

Burghardt et al. teaches progesterone, estradiol, 3βAdiol as estrogen receptor binding ligands (Table 2).

Barkheim et al. teaches that epiestriol has an ER-beta selective agonist potency.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used estriol or 3βAdiol, an ER-ligand in a method of reducing vascular reactivity from the teachings of Hermsmeyer and Burghardt et al. Hermsmeyer teaches progesterone, a steroid in coronary reactivity treatment and Burghardt et al. teaches the equivalence of estriol 3βAdiol and progesterone as estrogen receptor ligands. One having ordinary skill in the art would have been motivated in expectation of achieving similar or better therapeutic benefits in vascular reactivity conditions in administering

one estrogen receptor ligand such as estriol or 3βAdiol for another estrogen receptor ligand such as progesterone. It would have been obvious to one of ordinary skill in the art to administer epiestriol in reducing vascular reactivity in vascular smooth cells because epiestriol is known in the art to be an epimer of estriol and Barkeheim teaches that epiestriol is an estrogen receptor ligand. The reference Hermsmeyer teaches the amount of progesterone to be administered as 100 -4000 pg (for reducing vascular reactivity) which falls under the range of claimed amounts of 3βAdiol compounds. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to use such amounts of the claimed drug compounds in reducing vascular reactivity. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to administer in order to best achieve the desired therapeutic benefits. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of amount administered in a therapy would have been obvious at the time of applicant's invention.

Claims 5 and 6 claim the derivatives with 5α-androstane-3β,17 β-diol for the treatment of reducing vascular hyperreactivity. It is obvious that compounds with very close structural similarities will have similar utilities and hence the derivatives of 5α-androstane-3β,17 β-diol will function as estrogen beta-receptor agonists. The examiner would like to point out that a prima facie case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An

obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991).

Claims 11, 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hermsmeyer (WO 98/37897) in view of Burghardt et al. (Biology of Reproduction, 36, 741-51, 1987) and Barkheim et al. (Molecular Pharmacology, 54, 105-112, 1998) as applied to claims 1, 2, 5-7, 9, 10, 13-16 above and further in view of Shaak et al. (U.S. 6,228,852).

Hermsmeyer, Burghardt et al. and Barkheim et al. teachings discussed as above. Burghardt et al. teaches progesterone, estradiol, 3βAdiol as estrogen receptor binding ligands.

The references do not teach administration of estrogen beta receptor agonist in concert with a hormone replacement therapy (HRT).

Shaak et al. teaches estrogen and progesterone in hormone replacement therapy (see abstract, claims).

It would have been obvious to one of ordinary skill in the art at the time of invention to use estrogen receptor ligands such as 3βAdiol in concert with HRT because both progesterone (natural progestin) an 3βAdiol are estrogen receptor ligands and one of ordinary skill in the art would have been motivated to use 3βAdiol in concert with HRT

in expectation of synergistic or additional therapeutic benefits in HRT as both compounds are estrogen receptor ligands.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hermsmeyer (WO 98/37897) in view of Burghardt et al. (Biology of Reproduction, 36, 741-51, 1987) and Barkheim et al. (Molecular Pharmacology, 54, 105-112, 1998) as applied to claims 1, 2, 5-7, 9, 10, 13-16 above and further in view of Meyers et al. (J Med Chem, 2001, 44, 4230-4251).

Hermsmeyer, Burghardt et al. and Barkheim et al. teachings discussed as above.

Burghardt et al. teaches progesterone, estradiol, 3βAdiol as estrogen receptor binding ligands.

The references do not teach diarylpropionitrile as the ER beta ligand in reducing vascular hyperreactivity conditions.

Meyers et al. teach diarylpropionitrile (DPN)as an ER-beta potency selective ligand (p 4231, para 2, lines 1-3).

It would have been obvious to one of ordinary skill in the art at the time of invention to administer diarylpropionitrile (DPN) in reducing vascular hyperreactivity. Burghardt et al. teaches progesterone, estradiol, 3βAdiol as estrogen receptor binding ligands and Myers teach DPN as an estrogen receptor ligand. One having ordinary skill in the art would have been motivated in expectation of achieving similar or better therapeutic benefits in vascular reactivity conditions in administering one estrogen receptor ligand such as DPN for another estrogen receptor ligand such as progesterone.

Claims 1-3, 8, 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hermsmeyer (U.S. 6,056,972) in view of Meyers et al. (J Med Chem, 2001, 44, 4230-4251).

Hermsmeyer teach a method of reducing coronary artery reactivity and teaches that comprising administering estradiol 17β (via implants) (serum level, 104 +/- 10 pg/ml), an estrogen beta receptor ligand and progesterone (a progestin) reduced the incidence of coronary vasospasm in monkeys (col. 18, Table 3). The reference teaches using progesterone to treat coronary vasospasms and to prevent cardiovasular disorders including peripheral arterial vascular disease (Detailed Description, lines 1-5). The reference further teaches that the progesterone can be applied together with other hormone replacement therapy, particularly estrogen and the progesterone is believed not only to decrease coronary artery reactivity and counter the undesirable effects of estrogens that increase the risk of endometrial hyperplasia and cancer, but it also is believed to assist in retarding the development of osteoporosis and loss of cognitive function in post-menopausal or ovariectomized women (col.5, lines 25-33). The reference teaches that progesterone can be administered in various routes including oral, topical (as cream), nasal, vaginal, parenteral etc (see abstract, col. 9, lines 10-12). The reference teaches administration of 0.1 ng to less than 4 ng/ml of progesterone in treating coronary reactivity conditions (see claims 2-6).

The reference does not teach the use of selective estrogen beta receptor ligands such as diarylpropionitrile (DPN) as claimed by the applicant.

Meyers et al. teach estradiol and diarylpropionitrile as estrogen receptor ligands and DPN as an ER-beta potency selective ligand (p 4231, para 2, lines 1-3, Table 4).

It would have been obvious to one of ordinary skill in the art at the time of invention to administer diarylpropionitrile (DPN) for estradiol 17β from the teachings of Myers et al. Myers teach the DPN as an estrogen receptor ligand and has more potency towards ER β ligand. A person of ordinary skill in the art would have been motivated by the expectation of success and in achieving at least similar or superior therapeutic benefits in the treatment of vascular hyperreactivity compared to estradiol by substituting one estrogen receptor ligand for another (DPN for estradiol) in treating vascular hyperreactivity conditions.

Claims 4-6, 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hermsmeyer (U.S. 6,056,972) in view of Weihua et al. (PNAS, 2002, 99, 13589-94).

Hermsmeyer et al. teachings discussed as above.

The reference does not teach 5α-androstane-3β,17 β-diol or any of the derivatives claimed in reducing vascular hyperreactivity conditions.

Weihua et al. teaches 5α-androstane-3β,17 β-diol is an estrogen beta ligand and specifically, an estrogen receptor beta agonist (see Abstract).

It would have been obvious to one of ordinary skill in the art at the time of invention to administer 5α-androstane-3β,17 β-diol and its derivatives claimed for estradiol 17β in a method for reducing vascular hyperreactivity. A person of ordinary skill in the art would have been motivated to do so because by administering one estrogen receptor ligand for another one can expect success in regards to the

therapeutic treatment of vascular hyperreactivity treatment with similar or superior efficacy of the drug. The reference Hermsmeyer teaches the amount of progesterone to be administered as 100 -4000 pg (for reducing vascular reactivity) which falls under the range of claimed amounts of 3βAdiol compounds. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to use such amounts of the claimed drug compounds in reducing vascular reactivity. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to administer in order to best achieve the desired therapeutic benefits. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of amount administered in a therapy would have been obvious at the time of applicant's invention.

The compounds in claims 5 and 6 are derivatives of 5α-androstane-3β,17 β-diol and are rejected based on close structural similarity to 5α-androstane-3β,17 β-diol. It is obvious that compounds with very close structural similarities will have similar utilities and hence the derivatives of 5α-androstane-3β,17 β-diol will function as estrogen beta-receptor agonists. The examiner would like to point out that a prima facie case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See In

re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991).

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hermsmeyer (U.S. 6,056,972) in view of and in view of Barkheim et al. (Molecular Pharmacology, 54, 105-112, 1998).

The teachings of Hermsmeyer have been discussed in the 103(a) rejection set forth above.

The reference does not teach epiestriol in reducing the incidence or severity of vascular hyperreactivity.

Barkheim et al. teaches that epiestriol is an estrogen beta ligand and has an ER-beta selective agonist potency.

It would have been obvious to one of ordinary skill in the art at the time of invention to administer epiestriol for estradiol 17 β in a method for reducing vascular hyperreactivity. The motivation to do so is by administering one estrogen receptor ligand for another would provide similar or superior efficacy in the therapeutic treatment of vascular hyperreactivity.

Response to Arguments

Applicants' argue that the specification provides examples with ER-beta agonists and their activity and also examples show the effectiveness of epiestriol, DPN, 3βAdiol and estriol in vasospasms in vitro and estriol protection in vivo models and hence have provided sufficient data to establish that estrogen beta receptor agonists that are selective for ER-beta over ER-alpha to an extent that ER-alpha component is trivial for

the method of reducing vascular reactivity. In response, Applicants, have provided in vivo data for estriol for treating vasospasms and have provided comparison data for effects of estriol with 3βAdiol and epiestriol in vitro on Ca2+ responses in rhesus coronary VMC (example 9) and comparison data for estrogen beta receptor agonists (genistein, DPN) in measurement of estrogen receptor beta activity. However, the claims are broad with respect to all selective estrogen receptor beta agonist compounds that have a higher relative selectivity than does genistein for ER-beta compared to ER-alpha. There is a lot of undue experimentation involved in first checking the ER-beta activities of beta agonist compounds and then comparing their relative activity against genistein. As stated above there are quite a number of ER-beta ligands available and this does not include the ones yet to be discovered. After establishing the activity one of ordinary skill in the art would have to test the compounds whether they reduce the vascular hyperreactivity. There is prior art showing that ER-alpha agonists rapidly decrease pulmonary artery vasoconstriction by a nitric oxide mechanism (Lahm et al. (Am J Physiol Regal Integr Comp. Physiol. 295, 1486-93). Furthermore, the compounds need to be tested in vitro and in animal models whether the compounds work in concert with a hormone replacement therapy before administering the ER-beta agonist to a patient as there may be drug interactions involved in a combination therapy. Side effects of estriol are known in the art (http://www.patientsville.com/medication/estriol _side_effects.htm,Estriol Side Effects Report #5318690-8). The specification teaches only the administration of estriol to rhesus monkeys to show the effect of estriol in vasospasm. However, there are no models or working examples in the specification to

indicate that the drugs claimed in claim 1 will work in concert with hormone replacement therapy. Estrogen (http://www.medicinenet.com/estrogens-oral/article.htm#) document highlights the side effects and warns the patients of the potential risks of taking estrogens. Obviously, one of ordinary skill in the art would not only take note of such effects but to take precautions of adding another drug such as ER-beta agonist in the hormone replacement therapy (HRT). It would be an undue experimentation to a person of ordinary skill in the art to select a ER-beta agonist compound from the broadly claimed compounds and test in vitro and then in animal models and administer to a patient in reducing vascular reactivity and further use the same drug in concert for HRT after a series of experiments for HRT therapy. Accordingly, the claims as such are not enabled.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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